REMARKS

In an Office Action mailed March 26, 2002, the Examiner in charge of the application rejected pending Claims 1-10 and 13. The claims were rejected under 35 U.S.C. §112, first paragraph as allegedly being beyond the scope of enablement in the specification. The claims remained rejected under 35 U.S.C. §112, second paragraph for allegedly being vague and indefinite.

At the outset, the applicants and the undersigned thank Examiner Shukla for his helpful comments during a personal interview on August 9, 2002. The Examiner and the undersigned discussed all of the then-unresolved issues. In the interview, the Examiner stated his desire to ensure that any effect of the modulator recited in the claims was attributable to an effect by the modulator on the metalloprotease-thrombospondin (MPT) protein responsible for the migration activity of a developing gonadal cell. With this in mind, the applicants present the appended claims.

Each issue raised by the Examiner in the Office Action is addressed separately below. Reconsideration of the merits of this patent application is respectfully requested.

Rejections Under §112, first paragraph

The pending claims were rejected as being beyond the scope of enablement. The Examiner set forth in paragraph 6 a narrow claim said to be enabled by the specification. The claim addresses only the situation in which a polynucleotide that encodes the MPT protein is introduced into a GON-1 mutant that lacks gonadal cell migration such that the encoded protein is expressed in the gonadal distal tip cell. The proposed claim is inappropriate for at least two reasons. Applicants respectfully reiterate that the nematode itself can (but need not) comprise the MPT protein in the method and, further, that the MPT protein need not be expressed in the distal tip cell *per se*. This issue was discussed during the personal interview and it is believed that the Examiner has acknowledged the applicants' position as correct.

Amended Claim 1 addresses the Examiner's concerns. The amended claim recites that the migration activity is present only when the developing gonadal cell is under the influence of an MPT protein (even tough the method can be practiced on a nematode that initially lacks the migration activity). Moreover, the claim states that a modulator of the migration activity does not change the migration activity in a mutant nematode that comprises the developing distal tip cell but which does not comprise the MPT protein. Applicants believe that these changes specifically address the Examiner's contention that the method of Claim 1 "cannot distinguish that a modulator that affects the migration of the

gonadal cell does so by modulating the activity of a metalloprotease enzyme since the role of other enzymes or proteins cannot be ruled out." The role of such enzymes or proteins is explicitly not responsible for the effect in the method claimed in amended Claim 1. The claim also addresses the Examiner's concerns in the paragraph bridging pages 3 and 4 of the Office Action.

The application also specifically states that an MPT protein is essential for extension and expansion of the developing gonadal cell, depending upon whether the protein is expressed in the cell itself or in muscle cells. See, e.g., page 5, lines 8-18 *et seq*. As an aside, the specification describes in the first full paragraph on page 17 various methods for expressing the MPT protein of interest in both distal tip cells and in body wall muscle cells. In a similar vein, the Examiner asked the undersigned to note in the response that methods for introducing genes into *C. elegans* and for assaying the activity of a protein encoded by the introduced genes are routine in the art. The application specifically incorporates by reference *Caenorhabditis elegans*: Modern Biological Analysis of an Organism, Methods in Cell Biology, Volume 48, Epstein H. F. and D. C. Shakes, Eds., Academic Press (1995). The application at page 12, lines 15-27 indicates that this text describes routine methods for introducing modulators, including genes, into *C. elegans* and assessing the effects of said modulators.

It is believed, in summary, that all of the enablement issues are addressed by the amended claims for the reasons noted above and discussed in the interview.

Rejections Under §112, second paragraph

Claim 1 was rejected as vague and indefinite for lack of clarity as to whether the protein is an endogenous protein or has been introduced exogenously. As was discussed in the interview, either is appropriate. In the Office Action, the Examiner was of the opinion that the claims were enabled only for a nematode into which a polynucleotide encoding the protein was introduced. Applicants believe that the Examiner was persuaded that this need not be the case. Rather, the nematode used in the methods can produce the MPT protein even if not exogenously added. Also, the quality or quantity of the protein can vary and the protein need not be expressed from within a particular cell type. It is believed that the Examiner was particularly persuaded in view of the claim amendments that highlight the specificity of the method.

Claim 6 was rejected as vague and indefinite for use of the term "sufficiently close." The term no longer appears in the claims. Accordingly, the rejection is moot and should be withdrawn.

New Claims

New Claims 14-16 are added. These claims reflect the case in which the developing gonadal cell has no migration activity before the treating step, but where the treatment itself supplies an agent that confers migration activity as claimed. Claim 15 specifically contemplates the case in which the modulator is in fact acid that encodes a functional MPT protein. Claim 16 contemplates the case in which the modulator is an MPT protein that confers a migration activity to an otherwise non-migratory developing gonadal cell. Support for these claims is found in the prophetic example and elsewhere in the specification. Consideration of these new claims is respectfully requested.

Having responded to each issue raised by the Examiner, the applicants respectfully request reconsideration of the merits of this patent application.

Should any issue remain unresolved, the Examiner is invited to telephone the undersigned so that the issue can be addressed.

A petition for an extension of time for three months accompanies this response so this response will be deemed to have been timely filed. No fee other than the fee for extension of time is believed due, however, should any such fee be due, please charge the fee to Deposit Account No. 17-0055.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

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Date: September 26, 2002

Serial No.: 09/321,987

Group Art Unit: 1632

Filed: 05/28/1999

Examiner: Ram R. Shukla

For: AGENT AND METHOD FOR MODULATION OF CELL MIGRATION

File No.: 960296.95386

In the claims:

Please amend Claims 1 and 6-9 as follows:

1. (Amended three times) A method for [identifying in a nematode having a developing gonadal cell] selecting a modulator of a gonadal cell migration activity [of a protein] in [the] a nematode having a developing gonadal cell, [wherein the protein comprises a metalloprotease domain and a thrombospondin domain,] the nematode being selected from the group consisting of *C. elegans* and *C. briggsae*, the migration activity being selected from the group consisting of elongation and expansion, the migration activity being present only when the cell is under the influence of a protein that comprises a metalloprotease domain and a thrombospondin domain, the method comprising the steps of:

treating [the] a nematode with at least one potential modulator [of gonadal cell migration]; [and]

observing in the treated nematode a change in the migration [or shape] activity of the [developing gonadal] cell attributable to [modulation of the migration activity by] the at least one potential modulator, wherein the change is not observed after treatment with the potential modulator of a mutant of the nematode that comprises the cell but does not comprise the protein, wherein [a] the change [in the migration or shape of the developing gonadal cell] results in the [identification] selection of the modulator.

2. (Twice amended) A method as claimed in Claim 1 wherein [migration of the developing gonadal cell in the nematode before treatment] before the treating step the migration activity is absent or reduced relative to a wild type individual.

3. (Twice amended) A method as claimed in Claim 1 wherein the treating step restores or enhances [migration in the nematode relative to migration before the treating step] the migration activity.

4. (Twice amended) A method as claimed in Claim 1 wherein [migration of the developing gonadal cell in the nematode before treatment] before the treating step the migration activity is at a level of a wild type individual.

5. (Twice amended) A method as claimed in Claim 1 wherein the treating step reduces [migration in the nematode relative to migration before the treating step] the migration activity.

6. (Amended Three Times) A method as claimed in Claim 1, the protein being selected from the group consisting of a protein encoded by a native polynucleotide sequence, a protein encoded by a heterologous polynucleotide sequence introduced under transcriptional control of an active promoter into the nematode, a protein that shares at least 20% amino acid sequence identity in the metalloprotease and thrombospondin domains with either of the foregoing and that retains functional metalloprotease and thrombospondin domains, and a chimeric protein that retains functional metalloprotease and thrombospondin domains[, the heterologous polynucleotide sequence being under transcriptional control of a promoter active in a tissue located sufficiently close to the developing gonadal cell such that the protein can direct the cell to migrate].

10. (Amended) A method as claimed in Claim 6 wherein the protein is a truncated [relative to] form of a protein in a wild type individual.